onset several weeks after medication is begun. Shortly thereafter they become jaundiced and they produce dark urine. Liver function tests show increased levels of bilirubin and moderately elevated levels of transaminases. Liver biopsies show canalicular and hepaticocellular bile stasis. Liver tests in most patients with this condition revert to normal within several weeks after the cessation of therapy. In a few, however, abnormal liver function tests persist for longer periods.

Schaffner (151) has divided patients who become jaundiced with oral contraceptives into three groups. The first group includes women who have recurrent cholestasis of pregnancy; the jaundice in these patients may result from an idiosyncrasy of the liver to the agents. The second group of patients includes those who have cholestasis without evidence of cellular damage or hypersensitivity; a similar effect is produced in the jaundice associated with anabolic steroids, probably a direct action of the oral contraceptives on the bile secretory apparatus. The third group shows cellular injury or sensitivity to the drug.

Several studies (147) have shown that in some experimental animals, as well as the human being, the inhibition of bile transport seen with oral contraceptives is largely an effect of estrogen. Clinical studies have confirmed this concept, and recent investigations of low doses of progestins alone as contraceptives have shown little or no effect on bile transport or BSP excretion.

The oral contraceptives affect numerous enzyme systems other than those already mentioned (135). Among other effects are increases in activity of beta-glucuronidase and isocitrate dehydrogenase activities and decreases in activity of lactic dehydrogenase, alkaline phosphatase, and transaminase activities. Alteration in the serum naphthylamidase isozymes is thought to be one of the most sensitive indicators of disturbances in liver function caused by oral contraceptives (6). Stoll and coworkers (165) found a correlation between increases in the level of glutamic oxalacetic transaminase and the histological demonstration of damage to liver cells. They believe that this effect is caused by the progestin rather than the estrogen in the oral contraceptive. Recent reports (29, 154) that oral contraceptives increase ceruloplasmin-oxidase levels reflect the well-established observation that estrogen alone has this effect (57).

The recently observed apparent enhancement of hypertension by oral contraceptives in certain women may come about in part through the increase in serum-renin substrate levels. The estrogens in oral contrceptives may exert this effect by stimulation of the hepatic biosynthesis of this enzyme. Oral contraceptives also increase aldosterone levels. Such alterations have been postulated to compromise the ability of the renin-angiotensin-aldosterone mechanism to respond to normal physiological stimuli (97).

Another effect of the estrogen in oral contraceptives on enzyme systems concerns that metabolism of cortisone. It decreases the ability of the liver to extract cortisol from the blood (148) and is possibly related to the decrease in urinary excretion of cortisol and its metabolites (129) that results from administration of estrogen Sandberg has postulated that the progestins may also participate in displacing cortisol from transcortin. Although the true significance of these effects is unknown, their relation to pituitary function in particular should be investigated.

Several studies have demonstrated the effect of oral contraceptives on aminolevulinic acid (ALA) synthetase, an enzyme that participates in the production of heme. The enzyme is normally produced at a low rate by liver cells. Oral contraceptives have been shown to increase ALA synthetase levels as well as urinary coproporphyrin in a significant proportion of healthy women (26). The relation between this finding and the observation that oral contraceptives protect women with acute intermittent porphyria from attacks, is of considerable interest (127).

The effects of oral contraceptives on ALA synthetase may also be related to interference by oral contraceptives with the metabolism or detoxification of certain drugs. Their effect on ALA synthetase and on P-450-cytochrome, a hemoprotein located in the endoplasmic reticulum of the liver cell, may be related to alteration by oral contraceptives of the capacity of the liver to transform drugs into biologically inactive substances. Oral contraceptives appear to increase the detoxification of meperidine but to decrease the detoxification of normeperidine, a metabolic degradation product.